ELSEVIER

Seminars in
NUCLEAR
MEDICINE

Hepatic Cancers Overview: Surgical and Chemotherapeutic Options, How Do Y-90 Microspheres Fit in?

Jared H. Gans, MD,* Jeffrey Lipman, MD,† Yosef Golowa, MD,* Milan Kinkhabwala, MD,† and Andreas Kaubisch, MD‡

Hepatocellular cancer (HCC) is most common primary liver malignancy in adults. Treatment for HCC is a multispecialty undertaking, with surgical, locoregional, and systemic options available. Choice of treatment depends upon patient and disease factors. Surgical therapy, including resection and transplantation, is the primary curative treatment and is best suited to patients with early disease. More advanced disease may be amenable to locoregional therapies to "bridge" to transplantation, downstage disease, or as destination therapy for unresectable cases. These include percutaneous ablation, transarterial therapy, external radiation, and radioembolization with yttrium-90 conjugated beads. Patients with more advanced disease may benefit most from systemic chemotherapeutic or small molecule inhibitor options available, many of which have only been recently FDA approved. Immunotherapy is the newest component of HCC treatment. The Y-90 consultant should be familiar with all modalities of HCC treatment and the interplay between them.
Semin Nucl Med 49:170-181

Hepatocellular cancer (HCC) is the sixth most common cancer worldwide and third most common cause of cancer death.[1,2] Five-year survival is just over 10% without treatment and approximately 50% with treatment.[3,4] All current available treatments for HCC, including yttrium-90 (Y-90) radioembolization, are highly dependent on the patient. The primary risk factors for HCC include cirrhosis and viral hepatitis infection. Thus, treatment options for HCC may be limited at presentation due to the patient's baseline liver status making aggressive management unsafe.[5] Other determinants of treatment strategy include the tumor size, number of lesions, distribution of lesions, the presence of metastatic disease, and the patient's overall performance status.[6]

All of these components are taken into account in the two primary staging criteria utilized for HCC, the Chinese University Prognostic Index (CUPI) and the Barcelona Clinic Liver Cancer (BCLC) criteria.[7-9] The CUPI is a weighted score ranging from −7 to 12 dependent on TNM stage, symptoms upon presentation (or lack thereof), ascites, AFP level, total bilirubin level, and alkaline phosphatase level. This can be broken down into low-risk (−7 to 1), intermediate-risk,[2-7] and high-risk groups.[8-12] The BCLC criteria establish five major subgroups (0, A, B, C, and D) based off of patient performance status (as per the Eastern Cooperative Oncology Group [ECOG] system), tumor characteristics, and liver function. Current treatment guidelines utilize the patient's BCLC staging (Fig. 1).[10] Stage 0 is considered very early stage (<2 cm in size, ECOG 0, Child-Pugh A) and may be treated with curative resection or possibly ablation. Stage A is early stage (1-3 nodules less than 3 cm, ECOG 0, Child-Pugh A-B) can only be cured by liver transplantation. Stage B is intermediate (multinodular) and may be targeted with locoregional therapy, such as ablation, transarterial chemoembolization, radiation, or Y-90 radioembolization. Stage C is advanced (vascular invasion or nodal/extranodal metastases) and requires systemic therapy. Stage D is terminal (any tumor burden with Child-Pugh C cirrhosis or ECOG 3 or 4) and only supportive care is available. Familiarity with these guidelines and the other therapeutic modalities is important for the Y-90 consultant in patient evaluation and participating in interdisciplinary discussions regarding treatment.

*Department of Radiology, Montefiore Medical Center, Bronx, NY.
†Department of Surgery, Montefiore Medical Center, Bronx, NY.
‡Department of Medicine, Montefiore Medical Center, Bronx, NY.
Address reprint requests to Jared H. Gans, MD, Department of Radiology, Montefiore Medical Center, 111 East 210th Street, Bronx, NY 10467. E-mail: jgans@montefiore.org

 https://doi.org/10.1053/j.semnuclmed.2019.01.001
0001-2998/

Surgical Resection

Comprising eight total segments, with each receiving its own vascular supply and biliary drainage, Couinaud's 1957 description of hepatic anatomy still forms the basis of anatomic hepatic resection today.[11] Owing to the previously overlapping systems that were used to describe different liver resections, the Brisbane classification in 2000 standardized the nomenclature, dividing the liver into right and left hemilivers, followed by sectors, followed by segments, with appropriate resections based on these divisions (Fig. 2).[12,13] Knowledge of both the standard anatomy and common deviations is critical for appropriate hepatic resection, as variants are the norm, especially with respect to the arterial supply.[14] Quality preoperative cross-sectional imaging and intraoperative ultrasonography are important adjuncts to safe resection.

In anatomic liver resections, resections are carried along the planes separating Couinaud segments with ligation of the segments' specific inflow and outflow. While this oncologic strategy removes the entire section of liver theoretically affected by malignant degeneration, with better control of micrometastases, it sacrifices a larger amount of hepatic parenchyma compared to a nonanatomic resection (ie, a parenchymal resection to clear tumor margins). While conclusions have been mixed,[15] recent data, including a prospective randomized trial, have suggested improved disease-free survival after anatomic resections, especially in small lesions.[16,17]

The ultimate goal of hepatic resection in hepatocellular carcinoma is adequate resection of the involved parenchyma with preservation of sufficient liver remnant (ie, future liver remnant) to prevent postoperative liver failure, the leading cause of perioperative mortality.[18]

As the portal circulation is valveless, resections of hepatic parenchyma lead to increased pressure in the remaining portal veins until the remnant liver hypertrophies postoperatively. As long as the remnant liver is sufficient to handle the increased pressure, postoperative liver failure will not develop. Generally, a remnant size of at least 20%-25% of a healthy liver or greater than 40% of a cirrhotic liver is considered sufficient.[19,20] Size can be estimated by either cross-sectional volumetry calculated from CT or MRI, or functional liver studies such as indocyanine green (ICG) clearance or hepatobiliary scintigraphy with single-photon emission computed tomography (SPECT).[21]

Tumoral factors that favor successful liver resection as a treatment modality include solitary lesions, or multiple lesions with none greater than 5 cm (American Joint Committee on Cancer T1 and T2). These tumors should not

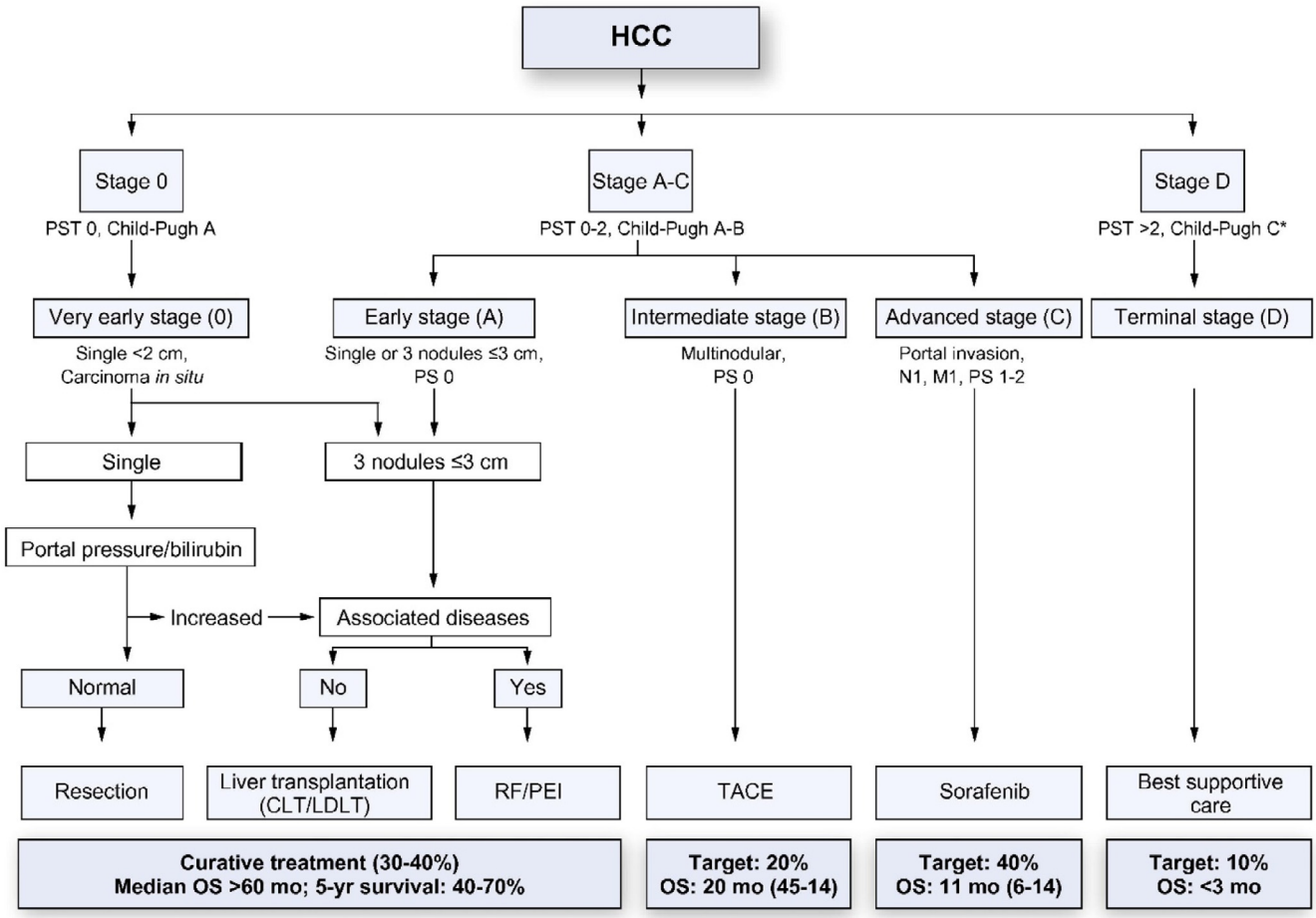

Figure 1 Barcelona Clinic Liver Classification (BCLC) staging system with management strategy based on BCLC staging. Reprinted from ref 10, with permission from Elsevier.

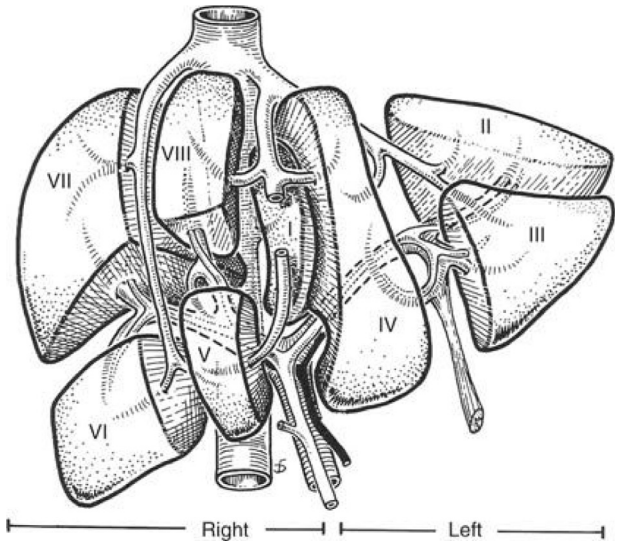

Figure 2 The segments of the liver and vasculobiliary anatomy as first described by Couinaud et al (1957). From ref 13, license at https://creativecommons.org/licenses/by-nc-sa/3.0/.

involve major portal or hepatic veins, and should not directly invade viscera other than the gallbladder. Large tumor size has been shown to portend a worse prognosis.[22,23] Solitary lesions greater than 5 cm are thought by some surgeons to preclude resection, but size itself is not a pure determinant for selection. Published by the International Cooperative Study Group on HCC, a 2005 retrospective study of 300 patients who underwent resection for tumors greater than 10 cm showed an acceptable 5-year survival of greater than 25%.[24] In 2013, the same group published another retrospective analysis which followed outcomes of major hepatectomy (defined as resections of greater than four segments) from 1981 to 2008. They noted significant improvements in both postoperative and 5-year mortality over the examined time period. The median tumor size was 10 cm, suggesting that if required, major hepatectomy has become increasingly justified.[25] Additional studies have demonstrated similar safety with resection of large lesions in patients with adequate functional liver reserve.[26,27]

Hepatic factors favoring resection as a primary treatment modality include patients with no stigmata of portal hypertension; although some patients with Child-Pugh class A cirrhosis can be candidates for small resections. The American Association for the Study of Liver diseases recommends resection as primary therapy for patients with well-preserved liver function and T1 or T2 lesions.[28] Similarly, the European Association for the Study of the Liver recommends resection for patients with solitary tumors and very well-preserved liver function, indicated by a normal serum bilirubin, platelet count greater than 100,000, and a hepatic venous pressure gradient less than 10 mm Hg.[10]

Portal vein embolization and portal vein ligation are two strategies to promote hypertrophy of the anticipated future liver remnant generally used in preparation for right hepatectomies. Typically, portal vein embolization is percutaneously accomplished via a direct transhepatic puncture with subsequent embolization of the lobe to be resected.[29] Portal vein ligation involves the surgical exposure and ligation of the desired portal vein via either laparotomy or laparoscopy.[30] Comparisons between the two have yielded similar increases in future liver remnants,[31,32] with most centers favoring portal vein embolization due to its minimally invasive nature.

Liver Transplantation

In patients who are not a candidate for resection, liver transplantation represents the only other potentially curative modality in hepatocellular carcinoma. Transplantation serves two purposes: resection of the tumor and replacement of the dysfunctional liver. While initial experiences yielded poor survival and recurrence rates,[33] Mazzaferro's 1996 groundbreaking study established transplant as an effective treatment for patients with cirrhosis and small, unresectable hepatocellular carcinomas.[34] When pathologic specimens met their predetermined criteria, 4-year survival exceeded 80%. This study produced the Milan criteria, which restricts transplantation to patients with a single lesion less than 5 cm, or up to three separate lesions with none larger than 3 cm, with no evidence of vascular invasion, and no regional nodal or distant metastases. The United Network for Organ Sharing still uses these criteria to select suitable patients for transplantation. As patients with HCC meeting criteria for transplantation often have well-compensated liver disease, and thus a lower Model for end-stage liver disease score than patients with purely advanced liver disease, exception points are allocated to equalize the risk of death from HCC progression on the waiting list.[35]

While no large randomized controlled trials exist, retrospective studies suggest that liver transplantation yields survival that is equivalent[36,37] or superior to resection.[38,39] Limited by the availability of organ donation, however, studies comparing resection to transplantation capture only patients who receive allografts, and fail to account for mortality on waiting lists.

There are multiple strategies to increase the supply of available livers for transplantation including the use of living donor partial livers, the predominant method of liver transplantation used in Asia. Biologically, there exists a fear that a regenerating partial liver graft is a source of HCC recurrence and yields lower disease-free survival than deceased donor grafts,[40] but multiple studies have shown equivalent outcomes.[41,42] The use of deceased donor livers after cardiac death yields a recognized increase in biliary complications compared to donor livers after brain death,[43] and in patients with HCC has been associated inferior oncological outcomes as well as overall survival.[44] One must compare, however, these theoretically poorer outcomes with the risk of death and disease progression on the waiting list.

Finally, many centers consider the Milan criteria too strict given modern surgical and medical management. For example, The University of California, San Francisco criteria accepts patients with single tumors $\leq$6.5 cm, three tumors with each $\leq$4.5 cm, with a total tumor diameter $\leq$8 cm. A study of 168 patients meeting these criteria yielded 5-year disease-free

survival of 81%, with no difference between the subgroups meeting UCSF criteria but exceeding Milan criteria vs those meeting Milan criteria.[45] Currently, the American Association for the Study of Liver diseases recommends consideration for transplantation only if patients are successfully downstaged to within the Milan criteria using the techniques below.[27]

Percutaneous Ablation

Percutaneous image-guided tumor ablation is a targeted locoregional therapy for destroying the tumor utilizing a variety of methods. These include percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), cryoablation, and microwave ablation (Fig. 3)[46]. PEI was the first image-guided percutaneous therapy for HCC with the benefit of increased survival and biochemical response compared to published natural history for the disease.[47,48] RFA destroys tumor cells using heat generated from an alternating electrical current. It was demonstrated to be more effective than PEI for both local control and survival, though requires general anesthesia due to the pain associated with thermal ablation.[49,50] For patients with early stage disease (BCLC 0 or A), ablation with RFA has been shown in randomized controlled trials to have similar outcomes to surgery in small tumors and hence is a viable first-line option for these patients.[51,52] While image-guided RFA carries the distinct advantage of being minimally invasive, other studies have shown RFA to however be inferior for local disease control when compared to resection.[53-55] RFA may alternatively be used to "bridge" transplant candidates to keep them in transplant criteria until an organ becomes available.[56] In patients with more advanced HCC, RFA may be used to potentially downstage to transplant status or for palliation.[57-59] RFA has the disadvantages of reduced effectiveness in certain tissues with low impedance (such as lung) and that overheating locally can increase tissue impedance and limit maximum temperature.[60,61] Additionally, flowing adjacent blood can reduce heat generated by ablation, known as the heat sink effect, which reduces effectiveness in lesions larger than 3 cm.[62]

Cryoablation alternatively utilizes compressed low-temperature gases (nitrous oxide or argon) delivered percutaneously to freeze the tumor. It may require multiple freeze-thaw cycles to generate tumor death, but can be done under moderate sedation and has less risk of damaging adjacent structures such as the gallbladder.[60] Early experience with cryoablation for HCC was promising, with comparable tumor response and survival to RFA in long-term studies and a multicenter randomized trial.[63,64] This optimism for cryoablation was blunted however as bleeding complications arose (cryoablation does not have the cauterizing effect thermal ablation has) and rare but frequently fatal reported cases of "cryoshock," a syndrome of multiorgan failure and disseminated intravascular coagulation similar to that produced by sepsis but without a clear infectious source.[65,66] Cryoablation has since fallen out of favor for hepatic malignancies, though is still often used for renal and musculoskeletal malignancies.[60]

Microwave ablation uses an electromagnetic field generated by a percutaneously placed antenna instead of electromagnetic current (as in RFA). Microwave ablation can produce higher temperatures in a greater variety of tissues than RFA and

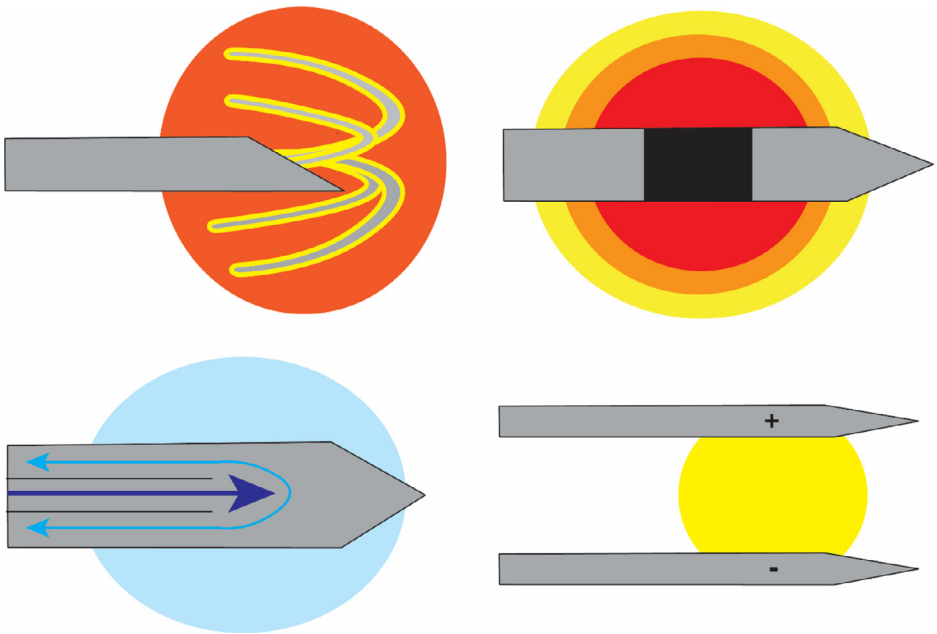

Figure 3 Ablation probe types. RFA probes produce thermal cell death utilizing transmitted current, commonly through an expanding electrode array (upper left). Microwave probe tips utilize water molecule friction generated by an electromagnetic field from an antenna near the probe tip (upper right). Cryoablation utilizes compressed nitrous oxide or argon gas released near the probe tip to generate an ablative iceball (lower left). IRE utilizes high voltage, low energy direct current pulses between monopolar probes to induce apoptosis through permanent disruption of tumor cell membranes (lower right).

avoids the heat sink effect, allowing effective treatment in larger lesions than RFA.[60-62] Limited prospective randomized data are available comparing microwave ablation to RFA. An early randomized trial of 72 patients demonstrated similar outcomes in small HCC lesions for RFA and microwave ablation; however, microwave ablation required more treatment sessions to achieve tumor response.[67] A more recent randomized multicenter trial of 152 patients demonstrated similar results overall for both methods.[68] The choice of one method over the other is a point of active controversy and depends on the clinical scenario.

The newest method of percutaneous tumor ablation is irreversible electroporation (IRE). IRE utilizes high voltage, low energy direct current pulses delivered between at least two monopolar electrodes to induce cell permeability and apoptosis to a defined volume.[69] IRE has been successfully used in HCC lesions not amenable to thermal ablative techniques or surgery due to tumor location near other vital structures.[70] This more local effect may also allow for effective tumor treatment in patients with more advanced cirrhosis (Child-Pugh B) who cannot tolerate thermal ablation.[71] However, no randomized comparative data exist at this time for IRE use in HCC.

Transarterial Chemotherapy

An alternative locoregional therapy to treat hepatic malignancies is the transarterial approach directly to arteries feeding the tumor. "Bland" embolization of hepatic tumors with only embolic materials induces hypoxia and tumor death in hypervascular tumors such as HCC, which has preferential blood uptake from the arterial circulation compared to the normal liver parenchyma that relies more heavily on the portal circulation.[72,73] Transarterial chemoembolization (TACE) is a method whereby chemotherapy is delivered intra-arterially in the form of a drug cocktail containing chemotherapy (doxorubicin as single agent or a chemotherapy cocktail), radiopaque ethiodized oil such as Lipiodol (Guerbet LLC, Bloomington, IN), and embolic material such as polyvinyl alcohol particles or microspheres. The ethiodized oil utilized in this conventional TACE (cTACE) results in better drug delivery to tumor cells and the embolic agent reduces washout and systemic dose while simultaneously inducing tumor hypoxia.[74] TACE may be used to bridge patients to transplant or downstage unresectable patients to potential surgical candidates.[57,75] Conventional TACE has also been shown to demonstrate tumor response and improve survival in patients with unresectable HCC in randomized controlled clinical trials and is hence a standard of care treatment for these patients.[76-78] Unfortunately, recurrence after TACE is high and multiple sessions of TACE may be necessary for a single lesion.[79,80] Additionally, the potential of embolic damage to the liver and systemic chemotherapeutic toxicity makes TACE unsuitable for patients with advanced cirrhosis.[81]

A newer method of TACE involves the use of chemotherapy (usually doxorubicin) loaded embolic beads, known as drug-eluting bead TACE (DEB-TACE).[82] DEB-TACE beads remain trapped in the tumor vasculature and deliver chemotherapy locally at a sustained rate, with decreased theoretical risk of hepatic and systemic dose compared to cTACE.[83] The Precision V study of 212 patients with unresectable HCC randomized patients to receive cTACE or DEB-TACE demonstrated no significant differences in tumor control between the two therapies but showed reduced liver and systemic toxicity in the DEB-TACE group.[84] Some data suggest that DEB-TACE may act primarily as an embolic rather than a chemotherapeutic. A randomized trial of 101 patients have compared DEB-TACE to bland embolization without chemotherapy demonstrated no difference in clinical survival, though imaging tumor response was improved with DEB-TACE.[85] Another trial of 101 patients comparing the two therapies demonstrated no difference in imaging response or survival.[86] While few centers utilize bland embolization, the choice of cTACE or DEB-TACE at this time is institution specific as no randomized data at this time demonstrate a survival advantage of one strategy over the other.[87]

TACE may be combined with ablation to successfully treat larger tumors greater than 2 cm in size.[88,89] A randomized trial of 95 patients treated with either RFA or TACE-RFA in patients with tumors less than 7 cm in size demonstrated improved overall survival and recurrence-free survival with TACE-RFA.[90] Utilizing microwave ablation instead of RFA with TACE is feasible and likely equivalent.[91,92] Preablation TACE provides an additional advantage of radiographically staining tumors with lipiodol or retained contrast for later improved targeting during ablation.[84]

External Beam Radiation

External beam radiation therapy represents a noninvasive locoregional therapy for hepatic malignancies. In unresectable HCC who progressed after TACE, prior retrospective studies showed conventional local radiotherapy resulted in modest tumor response in the majority of patients.[93] Toxicities include thrombocytopenia, and gastrointestinal toxicities such as ulcers, and radiation induced liver disease (RILD). RILD may result in fulminant liver failure and the risk of RILD limited use of external beam radiation in hepatic malignancies until recently.[94]

Stereotactic body radiation therapy (SBRT) is a newer, more focused radiation therapy where three-dimensional conformal, noncoplanar radiation can be delivered in higher fractionated radiation doses to a specific liver lesion while limiting dose to adjacent normal liver tissue. This means SBRT allows for a higher potential tumor dose with a lower theoretical risk of RILD.[95] SBRT use for HCC is a relatively recent development, with promising early results for effectiveness in palliation of advanced disease and bridge to transplantation.[96,97] A retrospective cohort of inoperable HCC patients demonstrated no significant difference in survival for patients treated with RFA or SBRT, though SBRT demonstrated longer freedom from local progression in larger tumors.[98] Retrospective comparative data also suggest that

SBRT may have similar outcomes to TACE for survival and 1-year local tumor control.[99] Conversely, a propensity-matched retrospective review of the National Cancer Database comparing SBRT to RFA for nonsurgical early HCC demonstrated increased survival in the RFA group.[100] An intention-to-treat retrospective study of SBRT verses TACE or RFA as a bridge to transplant demonstrated no significant difference in surgical complication rates or post-transplant survival between the therapies, though there was an increased incidence of liver dysfunction after SBRT despite reduced prescribed radiation doses.[101] A randomized trial comparing TACE with external beam conformal radiotherapy to sorafenib for late-stage HCC with vascular invasion in 90 patients demonstrated increased progression-free survival at 3 months, increased median time to progression, and increased overall survival compared to sorafenib alone.[102] No randomized prospective data are currently published comparing SBRT alone to other locoregional therapies.

Systemic Treatment

Systemic treatment is indicated over locoregional therapies in patients with BCLC stage C disease.[10] A summary of all current available regimens is available in Table. Doxorubicin was the first systemic chemotherapy utilized for advanced, unresectable HCC which showed tumor response, but had significant cardiac toxicity when given systemically.[103] Later studies failed to demonstrate a clinically significant benefit at safe doses.[104,105] Oxaliplatin, however, demonstrated some improved outcomes in advanced HCC[106] and several regimens with modest efficacy incorporate oxaliplatin. These include oxaliplatin plus 5-fluorouracil with leucovirin (FOLFOX4),[107] capecitabine and oxaliplatin (XELOX)[108] and gemcitabine and oxaliplatin (GEMOX).[109,110] Even though traditional cytotoxic combination chemotherapy can be modestly effective, in patients with cirrhosis pre-existing cytopenias and delayed drug clearance severely limit the number of patients who might be considered good chemotherapy candidates. Little recent randomized multicenter controlled data exist on these chemotherapeutic regimens as the standard of care for advanced HCC is currently small molecule inhibitors.[111]

Sorafenib is a small molecule inhibitor of serine-threonine tyrosine protein kinases (Raf-1, B-Raf) involved in the angiogenesis, including vascular endothelial growth factor receptor and platelet-derived growth factor receptor beta. The SHARP trial, a multicenter double blinded, placebo-controlled trial of 602 Western patients with advanced HCC who were naïve to systemic treatment, demonstrated both increased median survival and time to radiologic progression of almost 3 months with sorafenib.[112] The multicenter, placebo-controlled ORIENTAL trial of 271 patients confirmed the effectiveness of sorafenib in HCC patients in a Asian-Pacific, predominantly hepatitis-B affected, patient population.[113] Side effects in both trials included hand-foot skin reactions, hypertension, diarrhea, and fatigue. As a result, sorafenib is currently the standard recommended first-line systemic therapy for advanced HCC.[10]

Sorafenib is however not beneficial for all patients with advanced HCC. Major tumor regressions are rare, and few patients experience long-term cancer control. Combination of sorafenib (in patients who can tolerate it) with cytotoxic

Table Systemic Therapies for HCC

Drug	Systemic Treatment	Phase of Trial	Study	N patients	N Treatment Arm	RR (%)	Median TTP (mo)	Median PFS (mo)	Median OS (mo)
Chemotherapy									
Doxirubicin	Primary	3	Lai et al 1988	106	60	8.0	NR	NR	2.4
	Primary	3	Gish et al 2007	445	222	4.0	2.1	2.3	7.4
FOLFOX4	Primary	3	Qin et al 2014	371	184	8.6	NR	2.4	5.9
XELOX	Primary	2	Boige et al 2007	50	50	7.0	NR	4.1	9.3
GEMOX	Primary	2	Louafi et al 2007	34	34	18.0	NR	6.3	11.5
Small molecule inhibitors									
Sorafenib*	Primary	3	Llovet et al 2008	602	299	2.0	5.5	NR	10.7
	Primary	3	Cheng et al 2009	271	150	3.3	2.8	NR	6.5
Lenvatinib*	Primary	3	Kudo et al 2018	954	478	40.6	7.4	7.4	13.6
Regorafenib*	Secondary	3	Bruix et al 2017	573	374	11.0	3.2	3.1	10.6
Ramucirumab	Secondary	3	Zhu et al 2015	565	283	7.0	3.5	2.8	9.2
	Secondary, AFP >400 ng/mL	3	Zhu et al 2018	292	197	4.6	NR	2.8	8.5
Cabozantinib*	Secondary	3	Abou-Alfa et al 2018	707	470	4.0	NR	5.2	10.2
Immune checkpoint inhibitors									
Nivolumab*	Secondary	1/2	El-Khoueiry et al 2017	48 (dose expansion)	48	15.0	3.4	NR	15
	Secondary			214 (dose escalation)	214	20.0	4.1	NR	NR
Pembrolizumab*	Secondary	2	Zhu et al 2018	104	104	17.0	4.1	4.1	12.9

NR, not reported.
*FDA approved for HCC.

chemotherapy such as GEMOX may increase overall response rates.[114] Survival benefit has not been shown in patients with more severe cirrhosis (Child-Pugh B or greater), and side effects are more prominent in these patients[115,116]

To date, sorafenib has not been effective at preventing liver cancer recurrence after TACE or surgical resection. The STORM phase 3 multicenter, placebo-controlled trial of sorafenib after radiologically successful radiofrequency ablation or surgery demonstrated no difference in median survival or recurrence from placebo.[117] Two later placebo-controlled trials of sorafenib with TACE for HCC, the SPACE and TACE 2 trials, showed no difference in survival or tumor progression compared to TACE alone.[118,119] Increased toxicity was seen with the concomitant use of sorafenib and SBRT for HCC in a phase I trial.[120] Thus, the use of sorafenib in patients able to undergo locoregional therapy is controversial and likely not indicated in most patients at this time.

New Small Molecule Inhibitors

In recent years, the landscape of systematic treatment has changed, with newer agents FDA approved and clinically available.[121] A number of multikinase inhibitors (including sunitinib,[122] brivanib,[123] erlotinib,[124] and linifanib[125]) were tested against sorafenib in large randomized clinical trials and failed to prove superior. Lenvatinib is an oral multikinase inhibitor of VEGF, fibroblast growth factor, platelet-derived growth factor, as well as RET and KIT kinases. In the REFLECT randomized trial of 954 patients who received lenvatinib or sorafenib as first-line therapy for HCC,[124] there was no significant difference in median survival time, establishing noninferiority. However, there was a significantly improved response rate (18.8% vs 6.5%), and increased time to progression in the lenvatinib group (8.9 months) compared to the sorafenib month (3.7 months). Hypertension is a more prominent side effect of lenvatinib, hand-foot skin reactions are more severe with sorafenib.[126] These studies have led to FDA approval of lenvatinib as a first-line treatment in HCC. It is the only systemic small molecule inhibitor besides sorafenib to have this approval, and the first therapy to receive such approval in nearly a decade.

Other small molecule inhibitor drugs have only been studied in patients who failed sorafenib. Regorafenib is another tyrosine kinase inhibitor involved in angiogenesis as well as stromal proliferation with a similar side effect profile to sorafenib.[127] Second-line treatment with regorafenib demonstrated an increase in overall survival (10.6 months compared to 7.8 months with placebo) in patients who failed sorafenib with Child-Pugh A liver function in the parallel double-blinded randomized RESOURCE trial of 573 patients.[128] This lead to FDA approval of regorafenib for HCC as a second-line therapy.

Ramucirumab is a recombinant monoclonal antibody and VEGF receptor-2 antagonist. The REACH trial, a phase 3 double-blinded placebo-controlled trial of 565 patients who failed sorafenib demonstrated no improvement in survival with ramucirumab.[129] However, subgroup analysis demonstrated that ramucirumab had some effect on AFP levels and patients with greater AFP response had significantly greater radiographic response to treatment.[130] The follow-up REACH-2 trial of 292 patients with HCC who had progressed following sorafenib with Child-Pugh A cirrhosis and AFP levels >400 demonstrated a survival benefit with ramucirumab of 8.5 months compared to 7.3 with placebo. There was similar benefit for progression-free survival.[131]

Cabozantinib is a tyrosine kinase inhibitor to multiple VEGF growth factor receptors. In the CELESTIAL trial of 707 HCC patients who had progressed after prior systemic therapy randomly assigned to cabozantinib or placebo, cabozantinib resulted in approximately 2 months greater median overall survival and 3 months greater progression-free survival compared to placebo. Side effects included hand-foot skin reactions, hypertension, diarrhea, fatigue, and elevated liver enzymes.[132] Cabozantinib is now FDA approved for second line therapy in HCC.

Immunotherapy

Immunotherapy represents another potential strategy for HCC treatment. HCC evades the immune system through numerous postulated mechanisms, including tumor-associated regulatory T-cells and adjacent tolerogenic macrophages within the liver.[133] Early efforts to utilize the immune system in HCC treatment used activated autologous lymphocytes given after surgery in an attempt to reduce recurrence.[134] Another attempt involved the use of Interferon alpha-beta, which was not well tolerated in cirrhotic patients and did not produce increased survival.[135] While numerous immunologic therapies and targets for HCC were postulated, none of these efforts lead to reproducible results and widespread adoption until recent development of immune checkpoint inhibitors.[136]

One such inhibitor is Nivolumab, an IgG4 monoclonal antibody to PD-1 (programmed cell death receptor-1). PD-1 is an inhibitory receptor seen on T-cells and activated B-cells. The ligand for PD-1 (PD-L1) is overexpressed in HCC and increased expression is inversely correlated with survival.[137,138] Nivolumab has been shown to be safe in patients with advanced HCC, whether on sorafenib or not.[139] The Checkmate 040 dose escalation study of 264 patients demonstrated a 9-month overall survival rate of 74% across all doses.[140] Subgroup analysis demonstrated durability of treatment response in patients previously treated with sorafenib who initially responded to nivolumab.[141] This data has led to FDA approval for nivolumab as a second-line therapy for advanced HCC who failed sorafenib. Pembrolizumab, another PD-1 inhibitor, is currently in trial for patients who failed sorafenib.[142] Based on outcomes (17% response rate, 4.9-month progression-free survival, OS 12.9 months) pembrolizumab has also attained FDA approval for second-line treatment of patients after Sorafenib failure.[143]

Combination of checkpoint inhibitors with directly injected genetically engineered herpes virus currently used to treat

melanoma (Talimogene laherparepvec or T-VEC) is also being studied in HCC as well as for metastatic liver lesions.[144] The T-VEC is hypothesized to produce more cell death and cascade an immune reaction strengthened by the PD-L1 inhibition. An alternative strategy is targeting multiple components of tumor immune dysregulation. Laboratory models have shown that regulatory T-cells derived from HCC inhibit immune targeting of tumor cells by the CTLA-4 molecule.[145] The HIMALAYA study will administer both a PD-L1 inhibitor (durvalumab) and a CTLA-4 inhibitor (tremelimumab) into HCC patients who failed sorafenib.[144] Alternative strategies for future immunotherapy may involve cell-based therapies, such as tumor-derived vaccine therapies or induced natural killer cells, which have been used as adjuvant therapies after surgery or radiofrequency ablation, respectively.[146,147]

Preliminary data from trials combining angiogenesis inhibitors with immune checkpoint inhibitor drugs (atezolizumab and bevacizumab,[148] pembrolizumab and lenvatinib[149]) has shown tantalizingly high response rates, but clinical benefit remains to be confirmed in larger clinical trials.

Where Does Yttrium-90 Fit in?

Locoregional therapy with Y-90 involves the use of Y-90-tagged microspheres delivered transarterially directly to the tumor, a treatment termed radioembolization. Y-90 may be delivered globally to the liver in advanced liver disease with multifocal nodules or portal vein thrombosis not amenable to other locoregional therapies.[150] Y-90 may be utilized locally in the liver in the form of radiation segmentectomy, which has shown comparable survival outcomes to TACE and potentially improved time to local progression.[151-153] The ablative potential of radiation segmentectomy in producing local control has been similar to even TACE combined with ablation in one propensity-matched retrospective study of unresectable tumors up to 3 cm in size.[154] The potential use of this alternative locoregional therapy in conjunction with surgical and medical systemic therapies is of high importance to the physician performing radioembolization.

In terms of surgical treatment, Y-90 is of greatest interest as a bridge to transplantation or for downstaging to resection or transplant. Radiation segmentectomy may even be superior to TACE in downstaging patients to transplantation.[155] Recently, radiation lobectomy, or delivery of an ablative Y-90 dose to an entire hepatic lobe, has been described as a method to both locally treat a tumor and hypertrophy the contralateral lobe prior to partial hepatectomy.[156] Radioembolization additionally does not increase surgical morbidity. In a comparative study of 172 patients undergoing TACE or radioembolization for early HCC prior to transplantation, recurrence-free survival after transplant was similar.[157] Ninety-day surgical complications after Y-90 treatment were shown to be at the expected levels of treatment naïve patients.[158] Thus, Y-90 appears to play a symbiotic role with surgical treatment.

For patients with locally advanced cancer not eligible for other therapies, Y-90 has been shown in a multicenter trial (SIRveNIB) of 360 BCLC B and C patients to have similar tumor response with fewer adverse events compared to treatment with sorafenib.[159] The SARAH trial of 467 patients demonstrated no significant difference in survival or progression-free survival between the two therapies; however, patient tolerability of treatment was greater in the Y-90 group.[160] Thus, Y-90, while more invasive, may be an option for patients who may not tolerate sorafenib. At the same time, the judicial use of Y-90 simultaneously with sorafenib and other systemic therapies in patients with advanced HCC is considered safe based off of published data.[161,162] However, caution is advised in early HCC as sorafenib may increase post-transplant complications when used concomitantly with Y-90.[163] No major studies have been performed comparing or combining the newer small molecule inhibitors with Y-90 treatment.

Immunotherapy may complement Y-90 treatment. Radioembolization is thought to increase antigen presentation and hence T-cell activation, which could potentiate the effect of immunomodulatory drugs such as nivolumab.[164] A phase 2 trial of nivolumab in Child-Pugh A HCC patients after radioembolization is underway, with an aim to enroll 40 patients.[165] The results of this trial may demonstrate a synergistic role of immunotherapy with Y-90 therapy.

The treatment of HCC requires review of patient and disease factors in the presence of a multispecialty effort. Surgical, locoregional, and systemic options must be available to provide the right treatment to the right patient. The Y-90 consultant must be aware of new developments of the other modalities to stay relevant and maintain perspective to choose the right candidate for radioembolization. The role of Y-90 in this environment will likely evolve along with the other treatments. The goal is the best result for the patient, whether that be resection, ablation, transplantation, or palliation.

References

1. Ferenci P, Fried M, Labrecque D, et al: World Gastroenterology Organisation Guideline. Hepatocellular carcinoma (HCC): A global perspective. J Gastrointestin Liver Dis 19:311-317, 2010
2. Jemal A, Bray F, Center MM, et al: Global cancer statistics. CA Cancer J Clin 61:69-90, 2011
3. Altekruse SF, McGlynn KA, Dickie LA, et al: Hepatocellular carcinoma confirmation, treatment, and survival in surveillance, epidemiology and end results registries, 1992-2008. Hepatology 55:476-482, 2012
4. Altekruse SF, McGlynn KA, Reichman ME: Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. J Clin Oncol 27:1485-1491, 2009
5. Pinter M, Trauner M, Peck-Radosavljevic M, et al: Cancer and liver cirrhosis: Implications on prognosis and management. ESMO Open 1: e000042, 2016
6. El-Serag HB, Marrero JA, Rudolph L, et al: Diagnosis and treatment of hepatocellular carcinoma. Gastroenterology 134:1752-1763, 2008
7. Forner A, Reig ME, Rodriguez de Lope C, et al: Current strategy for staging and treatment: The BCLC update and future prospects. Semin Liver Dis 30:61-74, 2010
8. Leung TWT, Tang AMY, Zee B, et al: Construction of the Chinese University Prognostic Index for hepatocellular carcinoma and comparison with the TNM staging system, the Okuda staging system, and the Cancer of the Liver Italian Program staging system. Cancer 94:1760-1769, 2002

9. Llovet JM, Brú C, Bruix J: Prognosis of hepatocellular carcinoma: The BCLC staging classification. Semin Liver Dis 19:329-338, 1999
10. EASL, EORTC. EASL-EORTC clinical practice guidelines: Management of hepatocellular carcinoma. J Hepatol 56:908-943, 2012
11. Couinaud C: Le foie: études anatomiques et chirurgicales. Masson & Cie, 1957
12. Pang YY: The Brisbane 2000 terminology of liver anatomy and resections. HPB 2:333-39, 2000. HPB 4:99-100, 2002
13. Primrose JN: Surgery for colorectal liver metastases. Br J Cancer 102:1313, 2010
14. Hiatt JR, Gabbay J, Busuttil RW: Surgical anatomy of the hepatic arteries in 1000 cases. Ann Surg 220:50, 1994
15. Marubashi S, Gotoh K, Akita H, et al: Anatomical versus non−anatomical resection for hepatocellular carcinoma. Br J Surg 102:776-784, 2015
16. Kudo A, Tanaka S, Ban D, et al: Anatomic resection reduces the recurrence of solitary hepatocellular carcinoma ≤5 cm without macrovascular invasion. Am J Surg 207:863-869, 2014
17. Feng X, Su Y, Zheng S, et al: A double blinded prospective randomized trial comparing the effect of anatomic versus non-anatomic resection on hepatocellular carcinoma recurrence. HPB 19:667-674, 2017
18. Mullen JT, Ribero D, Reddy SK, et al: Hepatic insufficiency and mortality in 1,059 noncirrhotic patients undergoing major hepatectomy. J Am Coll Surg 204:854-862, 2007
19. Vauthey J-N, Chaoui A, Do K-A, et al: Standardized measurement of the future liver remnant prior to extended liver resection: methodology and clinical associations. Surgery 127:512-519, 2000
20. Kishi Y, Abdalla EK, Chun YS, et al: Three hundred and one consecutive extended right hepatectomies: Evaluation of outcome based on systematic liver volumetry. Ann Surg 250:540-548, 2009
21. Serenari M, Collaud C, Alvarez FA, et al: Interstage assessment of remnant liver function in ALPPS using hepatobiliary scintigraphy: Prediction of posthepatectomy liver failure and introduction of the HIBA index. Ann Surg 267:1141-1147, 2018
22. Chang Y, Chung K, Chang Y, et al: Long−term survival of patients undergoing liver resection for very large hepatocellular carcinomas. Br J Surg 103:1513-1520, 2016
23. Zhou XD, Tang ZY, Yang BH, et al: Experience of 1000 patients who underwent hepatectomy for small hepatocellular carcinoma. Cancer 91:1479-1486, 2001
24. Pawlik TM, Poon RT, Abdalla EK, et al: Critical appraisal of the clinical and pathologic predictors of survival after resection of large hepatocellular carcinoma. Arch Surg 140:450-458, 2005
25. Andreou A, Vauthey J-N, Cherqui D, et al: Improved long-term survival after major resection for hepatocellular carcinoma: A multicenter analysis based on a new definition of major hepatectomy. J Gastrointest Surg 17:66-77, 2013
26. Allemann P, Demartines N, Bouzourene H, et al: Long-term outcome after liver resection for hepatocellular carcinoma larger than 10 cm. World J Surg 37:452-458, 2013
27. Shrager B, Jibara GA, Tabrizian P, et al: Resection of large hepatocellular carcinoma (≥10 cm): A unique western perspective. J Surg Oncol 107:111-117, 2013
28. Marrero JA, Kulik LM, Sirlin C, et al: Diagnosis, staging and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. Hepatology 68:723-750, 2018.
29. Avritscher R, de Baere T, Murthy R, et al: Percutaneous transhepatic portal vein embolization: Rationale, technique, and outcomes. Semin Intervent Radiol 25:132-145, 2008
30. Are C, Iacovitti S, Prete F, et al: Feasibility of laparoscopic portal vein ligation prior to major hepatectomy. HPB 10:229-233, 2008
31. Aussilhou B, Lesurtel M, Sauvanet A, et al: Right portal vein ligation is as efficient as portal vein embolization to induce hypertrophy of the left liver remnant. J Gastrointest Surg 12:297-303, 2008
32. Broering DC, Hillert C, Krupski G, et al: Portal vein embolization vs. portal vein ligation for induction of hypertrophy of the future liver remnant. J Gastrointest Surg 6:905-913, 2002
33. Ringe B, Pichlmayr R, Wittekind C, et al: Surgical treatment of hepatocellular carcinoma: Experience with liver resection and transplantation in 198 patients. World J Surg 15:270-285, 1991
34. Mazzaferro V, Regalia E, Doci R, et al: Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Eng J Med 334:693-700, 1996
35. Elwir S, Lake J: Current status of liver allocation in the United States. Gastroenterol Hepatol 12:166, 2016
36. Otto G, Heuschen U, Hofmann WJ, et al: Survival and recurrence after liver transplantation versus liver resection for hepatocellular carcinoma: a retrospective analysis. Ann Surg 227:424, 1998
37. Bismuth H, Chiche L, Adam R, et al: Liver resection versus transplantation for hepatocellular carcinoma in cirrhotic patients. Ann Surg 218:145, 1993
38. Adam R, Bhangui P, Vibert E, et al: Resection or transplantation for early hepatocellular carcinoma in a cirrhotic liver: Does size define the best oncological strategy? Ann Surg 256:883-891, 2012
39. Lee KK, Kim DG, Moon IS, et al: Liver transplantation versus liver resection for the treatment of hepatocellular carcinoma. J Surg Oncol 101:47-53, 2010
40. Kulik LM, Fisher RA, Rodrigo DR, et al: Outcomes of living and deceased donor liver transplant recipients with hepatocellular carcinoma: Results of the A2ALL cohort. Am J Transplant 12:2997-3007, 2012
41. Xiao GQ, Song JL, Shen S, et al: Living donor liver transplantation does not increase tumor recurrence of hepatocellular carcinoma compared to deceased donor transplantation. World J Gastroenterol 20:10953-10959, 2014
42. Ninomiya M, Shirabe K, Facciuto ME, et al: Comparative study of living and deceased donor liver transplantation as a treatment for hepatocellular carcinoma. J Am Coll Surg 220:297-304.e3, 2015
43. Maheshwari A, Maley W, Li Z, et al: Biliary complications and outcomes of liver transplantation from donors after cardiac death. Liver Transpl 13:1645-1653, 2007
44. Croome KP, Wall W, Chandok N, et al: Inferior survival in liver transplant recipients with hepatocellular carcinoma receiving donation after cardiac death liver allografts. Liver Transpl 19:1214-1223, 2013
45. Yao FY, Xiao L, Bass NM, et al: Liver transplantation for hepatocellular carcinoma: Validation of the UCSF-expanded criteria based on preoperative imaging. Am J Transplant 7:2587-2596, 2007
46. Lau WY, Lai EC: The current role of radiofrequency ablation in the management of hepatocellular carcinoma: A systematic review. Ann Surg 249:20-25, 2009
47. Shiina S, Tagawa K, Niwa Y, et al: Percutaneous ethanol injection therapy for hepatocellular carcinoma: Results in 146 patients. Am J Roentgenol 160:1023-1028, 1993
48. Shiina S, Tagawa K, Unuma T, et al: Percutaneous ethanol injection therapy of hepatocellular carcinoma: Analysis of 77 patients. Am J Roentgenol 155:1221-1226, 1990
49. Lencioni RA, Allgaier H-P, Cioni D, et al: Small hepatocellular carcinoma in cirrhosis: Randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. Radiology 228:235-240, 2003
50. Shiina S, Teratani T, Obi S, et al: A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma. Gastroenterology 129:122-130, 2005
51. Feng K, Yan J, Li X, et al: A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. J Hepatol 57:794-802, 2012
52. Lü MD, Kuang M, Liang LJ, et al: Surgical resection versus percutaneous thermal ablation for early-stage hepatocellular carcinoma: A randomized clinical trial. Zhonghua Yi Xue Za Zhi 86:801-805, 2006
53. Wang J-H, Wang C-C, Hung C-H, et al: Survival comparison between surgical resection and radiofrequency ablation for patients in BCLC very early/early stage hepatocellular carcinoma. J Hepatol 56:412-418, 2012
54. Jiang L, Yan L, Wen T, et al: Comparison of outcomes of hepatic resection and radiofrequency ablation for hepatocellular carcinoma patients with multifocal tumors meeting the Barcelona-clinic liver cancer stage a classification. J Am Coll Surg 221:951-961, 2015

55. Huang J, Yan L, Cheng Z, et al: A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. Ann Surg 252:903-912, 2010
56. Lu DSK, Yu NC, Raman SS, et al: Percutaneous radiofrequency ablation of hepatocellular carcinoma as a bridge to liver transplantation. Hepatology 41:1130-1137, 2005
57. Yao FY, Hirose R, LaBerge JM, et al: A prospective study on downstaging of hepatocellular carcinoma prior to liver transplantation. Liver Transplantation 11:1505-1514, 2005
58. Pompili M, Mirante VG, Rondinara G, et al: Percutaneous ablation procedures in cirrhotic patients with hepatocellular carcinoma submitted to liver transplantation: Assessment of efficacy at explant analysis and of safety for tumor recurrence. Liver Transpl 11:1117-1126, 2005
59. Tiong L, Maddern GJ: Systematic review and meta-analysis of survival and disease recurrence after radiofrequency ablation for hepatocellular carcinoma. BJS 98:1210-1224, 2011
60. Hinshaw JL, Lubner MG, Ziemlewicz TJ, et al: Percutaneous tumor ablation tools: Microwave, radiofrequency, or cryoablation—What should you use and why? Radiographics 34:1344-1362, 2014
61. Poulou LS, Botsa E, Thanou I, et al: Percutaneous microwave ablation vs radiofrequency ablation in the treatment of hepatocellular carcinoma. World J Hepatol 7:1054-1063, 2015
62. Pillai K, Akhter J, Chua TC, et al: Heat sink effect on tumor ablation characteristics as observed in monopolar radiofrequency, bipolar radiofrequency, and microwave, using ex vivo calf liver model. Medicine 94:e580, 2015
63. Wang C, Wang H, Yang W, et al: Multicenter randomized controlled trial of percutaneous cryoablation versus radiofrequency ablation in hepatocellular carcinoma. Hepatology 61:1579-1590, 2015
64. Wu S, Hou J, Ding Y, et al: Cryoablation versus radiofrequency ablation for hepatic malignancies: A systematic review and literature-based analysis. Medicine 94:e2252, 2015
65. Seifert JK, Morris DL: World Survey on the complications of hepatic and prostate cryotherapy. World J Surg 23:109-114, 1999
66. Rong G, Bai W, Dong Z, et al: Long-term outcomes of percutaneous cryoablation for patients with hepatocellular carcinoma within Milan criteria. PLoS One 10:e0123065, 2015
67. Shibata T, Iimuro Y, Yamamoto Y, et al: Small hepatocellular carcinoma: Comparison of radio-frequency ablation and percutaneous microwave coagulation therapy. Radiology 223:331-337, 2002
68. Vietti Violi N, Duran R, Guiu B, et al: Efficacy of microwave ablation versus radiofrequency ablation for the treatment of hepatocellular carcinoma in patients with chronic liver disease: A randomised controlled phase 2 trial. Lancet Gastroenterol Hepatol 3:317-325, 2018
69. Narayanan G, Froud T, Suthar R, et al: Irreversible electroporation of hepatic malignancy. Semin Intervent Radiol 30:67-73, 2013
70. Sutter O, Calvo J, N'Kontchou G, et al: Safety and efficacy of irreversible electroporation for the treatment of hepatocellular carcinoma not amenable to thermal ablation techniques: A retrospective single-center case series. Radiology 284:877-886, 2017
71. Bhutiani N, Philips P, Scoggins CR, et al: Evaluation of tolerability and efficacy of irreversible electroporation (IRE) in treatment of Child-Pugh B (7/8) hepatocellular carcinoma (HCC). HPB 18:593-599, 2016
72. Gaba RC, Schwind RM, Ballet S: Mechanism of action, pharmacokinetics, efficacy, and safety of transarterial therapies using ethiodized oil: Preclinical review in liver cancer models. J Vasc Interv Radiol 29:413-424, 2018
73. Maluccio MA, Covey AM, Porat LB, et al: Transcatheter arterial embolization with only particles for the treatment of unresectable hepatocellular carcinoma. J Vasc Interv Radiol 19:862-869, 2008
74. Ramsey DE, Kernagis LY, Soulen MC, et al: Chemoembolization of hepatocellular carcinoma. J Vasc Interv Radiol 13:S211-S221, 2002
75. Lesurtel M, Müllhaupt B, Pestalozzi BC, et al: Transarterial chemoembolization as a bridge to liver transplantation for hepatocellular carcinoma: An evidence-based analysis. Am J Transplant 6:2644-2650, 2006
76. Llovet JM, Real MI, Montaña X, et al: Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: A randomised controlled trial. Lancet 359:1734-1739, 2002
77. Lo C-M, Ngan H, Tso W-K, et al: Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 35:1164-1171, 2002
78. Llovet JM, Bruix J: Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. Hepatology 37:429-442, 2003
79. Woo HY, Jang JW, Choi JY, et al: Tumor doubling time after initial response to transarterial chemoembolization in patients with hepatocellular carcinoma. Scand J Gastroenterol 45:332-339, 2010
80. Llovet JM, Real MI, Montaña X, et al: Arterial embolization or chemoembolization versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomized controlled trial. Lancet 359:1734, 2002
81. Bruix J, Sherman M, Practice Guidelines Committee, et al: Management of hepatocellular carcinoma. Hepatology 42:1208, 2005
82. Vogl TJ, Naguib NN, Nour-Eldin N-EA, et al: Review on transarterial chemoembolization in hepatocellular carcinoma: Palliative, combined, neoadjuvant, bridging, and symptomatic indications. Eur J Radiol 72:505-516, 2009
83. Varela M, Real MI, Burrel M, et al: Chemoembolization of hepatocellular carcinoma with drug eluting beads: Efficacy and doxorubicin pharmacokinetics. J Hepatol 46:474-481, 2007
84. Veltri A, Moretto P, Doriguzzi A, et al: Radiofrequency thermal ablation (RFA) after transarterial chemoembolization (TACE) as a combined therapy for unresectable non-early hepatocellular carcinoma (HCC). Eur Radiol 16:661-669, 2006
85. Malagari K, Pomoni M, Kelekis A, et al: Prospective randomized comparison of chemoembolization with doxorubicin-eluting beads and bland embolization with beadblock for hepatocellular carcinoma. Cardiovasc Intervent Radiol 33:541-551, 2010
86. Brown KT, Do RK, Gonen M, et al: Randomized trial of hepatic artery embolization for hepatocellular carcinoma using doxorubicin-eluting microspheres compared with embolization with microspheres alone. J Clin Oncol 34:2046-2053, 2016
87. Facciorusso A, Di Maso M, Muscatiello N: Drug-eluting beads versus conventional chemoembolization for the treatment of unresectable hepatocellular carcinoma: A meta-analysis. Dig Liver Dis 48:571-577, 2016
88. Cheng B-Q, Jia C-Q, Liu C-T, et al: Chemoembolization combined with radiofrequency ablation for patients with hepatocellular carcinoma larger than 3 cm: A randomized controlled trial. JAMA 299:1669-1677, 2008
89. Morimoto M, Numata K, Kondou M, et al: Midterm outcomes in patients with intermediate-sized hepatocellular carcinoma. Cancer 116:5452-5460, 2010
90. Peng Z-W, Zhang Y-J, Chen M-S, et al: Radiofrequency ablation with or without transcatheter arterial chemoembolization in the treatment of hepatocellular carcinoma: A prospective randomized trial. J Clin Oncol 31:426-432, 2013
91. Ginsburg M, Zivin SP, Wroblewski K, et al: Comparison of combination therapies in the management of hepatocellular carcinoma: Transarterial chemoembolization with radiofrequency ablation versus microwave ablation. J Vasc Interv Radiol 26:330-341, 2015
92. Chen Q-W, Ying H-F, Gao S, et al: Radiofrequency ablation plus chemoembolization versus radiofrequency ablation alone for hepatocellular carcinoma: A systematic review and meta-analysis. Clin Res Hepatol Gastroenterol 40:309-314, 2016
93. Seong J, Park HC, Han KH, et al: Local radiotherapy for unresectable hepatocellular carcinoma patients who failed with transcatheter arterial chemoembolization. Int J Radiat Oncol Biol Phys 47:1331-1335, 2000
94. Toesca DA, Osmundson EC, Eyben RV, et al: Central liver toxicity after SBRT: An expanded analysis and predictive nomogram. Radiother Oncol 122:130-136, 2017
95. Feng M, Ben-Josef E: Radiation therapy for hepatocellular carcinoma. Semin Radiat Oncol 21:271-277, 2011
96. Sanuki N, Takeda A, Kunieda E: Role of stereotactic body radiation therapy for hepatocellular carcinoma. World J Gastroenterol 20:3100-3111, 2014

97. O'connor JK, Trotter J, Davis GL, et al: Long−term outcomes of stereotactic body radiation therapy in the treatment of hepatocellular cancer as a bridge to transplantation. Liver Transpl 18:949-954, 2012
98. Wahl DR, Stenmark MH, Tao Y, et al: Outcomes after stereotactic body radiotherapy or radiofrequency ablation for hepatocellular carcinoma. J Clin Oncol 34:452-459, 2016
99. Bettinger D, Gkika E, Schultheiss M, et al: Comparison of local tumor control in patients with HCC treated with SBRT or TACE: A propensity score analysis. BMC Cancer 18:807, 2018
100. Rajyaguru DJ, Borgert AJ, Smith AL, et al: Radiofrequency ablation versus stereotactic body radiotherapy for localized hepatocellular carcinoma in nonsurgically managed patients: Analysis of the National Cancer Database. J Clin Oncol 36:600-608, 2018
101. Sapisochin G, Barry A, Doherty M, et al: Stereotactic body radiotherapy vs. TACE or RFA as a bridge to transplant in patients with hepatocellular carcinoma. An intention-to-treat analysis. J Hepatol 67:92-99, 2017
102. Yoon S, Ryoo B, Lee S, et al: Efficacy and safety of transarterial chemoembolization plus external beam radiotherapy vs sorafenib in hepatocellular carcinoma with macroscopic vascular invasion: A randomized clinical trial. JAMA Oncol 4:661-669, 2018
103. Lai CL, Wu PC, Chan GC, et al: Doxorubicin versus no antitumor therapy in inoperable hepatocellular carcinoma. A prospective randomized trial. Cancer. 62:479-483, 1988
104. Sciarrino E, Simonetti RG, Moli SL, et al: Adriamycin treatment for hepatocellular carcinoma experience with 109 patients. Cancer 56:2751-2755, 1985
105. Gish RG, Porta C, Lazar L, et al: Phase III randomized controlled trial comparing the survival of patients with unresectable hepatocellular carcinoma treated with nolatrexed or doxorubicin. J Clin Oncol 25:3069-3075, 2007
106. Yen Y, Lim DW, Chung V, et al: Phase II study of oxaliplatin in patients with unresectable, metastatic, or recurrent hepatocellular cancer: A California Cancer Consortium Trial. Am J Clin Oncol 31:317-322, 2008
107. Qin S, Bai Y, Ye S, et al: Phase III study of oxaliplatin plus 5-fluorouracil/leucovorin (FOLFOX4) versus doxorubicin as palliative systemic chemotherapy in advanced HCC in Asian patients. J Clin Oncol 28:4008, 2010
108. Boige V, Raoul JL, Pignon JP, et al: Multicentre phase II trial of capecitabine plus oxaliplatin (XELOX) in patients with advanced hepatocellular carcinoma: FFCD 03-03 trial. Br J Cancer 97:862-867, 2007
109. Zaanan A, Williet N, Hebbar M, et al: Gemcitabine plus oxaliplatin in advanced hepatocellular carcinoma: A large multicenter AGEO study. J Hepatol 58:81-88, 2013
110. Louafi S, Boige V, Ducreux M, et al: Gemcitabine plus oxaliplatin (GEMOX) in patients with advanced hepatocellular carcinoma (HCC). Cancer 109:1384-1390, 2007
111. Le Grazie M, Biagini MR, Tarocchi M, et al: Chemotherapy for hepatocellular carcinoma: The present and the future. World J Hepatol 9:907-920, 2017
112. Llovet JM, Ricci S, Mazzaferro V, et al: Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 359:378-390, 2008
113. Cheng AL, Kang YK, Chen Z, et al: Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: A phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 10:25-34, 2009
114. Assenat E, Boige V, Thézenas S, et al: Sorafenib (S) alone versus S combined with gemcitabine and oxaliplatin (GEMOX) in first-line treatment of advanced hepatocellular carcinoma (HCC): Final analysis of the randomized phase II GONEXT trial (UNICANCER/FFCD PRODIGE 10 trial). Journal of Clinical Oncology 31:4028, 2013
115. Chiu J, Tang YF, Yao T-J, et al: The use of single-agent sorafenib in the treatment of advanced hepatocellular carcinoma patients with underlying Child-Pugh B liver cirrhosis. Cancer 118:5293-5301, 2012
116. Hollebecque A, Cattan S, Romano O, et al: Safety and efficacy of sorafenib in hepatocellular carcinoma: The impact of the Child-Pugh score. Aliment Pharmacol Ther 34:1193-1201, 2011
117. Bruix J, Takayama T, Mazzaferro V, et al: Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): A phase 3, randomised, double-blind, placebo-controlled trial. Lancet Oncol 16:1344-1354, 2015
118. Meyer T, Fox R, Ma YT, et al: Sorafenib in combination with transarterial chemoembolisation in patients with unresectable hepatocellular carcinoma (TACE 2): A randomised placebo-controlled, double-blind, phase 3 trial. Lancet Gastroenterol Hepatol 2:565-575, 2017
119. Lencioni R, Llovet JM, Han G, et al: Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: The SPACE trial. J Hepatol 64:1090-1098, 2016
120. Brade AM, Ng S, Brierley J, et al: Phase 1 trial of sorafenib and stereotactic body radiation therapy for hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 94:580-587, 2016
121. Raoul J-L, Kudo M, Finn RS, et al: Systemic therapy for intermediate and advanced hepatocellular carcinoma: Sorafenib and beyond. Cancer Treat Rev 68:16-24, 2018
122. Cheng A-L, Kang Y-K, Lin D-Y, et al: Sunitinib versus sorafenib in advanced hepatocellular cancer: Results of a randomized phase III trial. J Clin Oncol 31:4067-4075, 2013
123. Johnson PJ, Qin S, Park J-W, et al: Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: Results from the randomized phase III BRISK-FL study. J Clin Oncol 31:3517-3524, 2013
124. Zhu AX, Rosmorduc O, Evans T, et al: SEARCH: A phase III, randomized, double-blind, placebo-controlled trial of sorafenib plus erlotinib in patients with advanced hepatocellular carcinoma. J Clin Oncol 33:559-566, 2014
125. Cainap C, Qin S, Huang W-T, et al: Linifanib versus Sorafenib in patients with advanced hepatocellular carcinoma: Results of a randomized phase III trial. J Clin Oncol 33:172, 2015
126. Kudo M, Finn RS, Qin S, et al: Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: A randomised phase 3 non-inferiority trial. Lancet 391:1163-1173, 2018
127. Belum VR, Wu S, Lacouture ME: Risk of hand-foot skin reaction with the novel multikinase inhibitor regorafenib: A meta-analysis. Invest New Drugs 31:1078-1086, 2013
128. Bruix J, Qin S, Merle P, et al: Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 389:56-66, 2017
129. Zhu AX, Park JO, Ryoo B-Y, et al: Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): A randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol 16:859-870, 2015
130. Chau I, Park JO, Ryoo B-Y, et al: Alpha-fetoprotein kinetics in patients with hepatocellular carcinoma receiving ramucirumab or placebo: An analysis of the phase 3 REACH study. Br J Cancer 119:19-26, 2018
131. Zhu AX, Kang Y-K, Yen C-J, et al: REACH-2: A randomized, double-blind, placebo-controlled phase 3 study of ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma (HCC) and elevated baseline alpha-fetoprotein (AFP) following first-line sorafenib. J Clin Oncol 36:4003, 2018
132. Abou-Alfa GK, Meyer T, Cheng A-L, et al: Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. N Eng J Med 379:54-63, 2018
133. Obeid JM, Kunk PR, Zaydfudim VM, et al: Immunotherapy for hepatocellular carcinoma patients: Is it ready for prime time? Cancer Immunol Immunother 67:161-174, 2018
134. Takayama T, Sekine T, Makuuchi M, et al: Adoptive immunotherapy to lower postsurgical recurrence rates of hepatocellular carcinoma: A randomised trial. Lancet 356:802-807, 2000
135. Llovet JM, Sala M, Castells L, et al: Randomized controlled trial of interferon treatment for advanced hepatocellular carcinoma. Hepatology 31:54-58, 2000
136. Prieto J, Melero I, Sangro B: Immunological landscape and immunotherapy of hepatocellular carcinoma. Nat Rev Gastroenterol Hepatol 12:681, 2015
137. Gao Q, Wang X-Y, Qiu S-J, et al: Overexpression of PD-L1 significantly associates with tumor aggressiveness and postoperative recurrence in human hepatocellular carcinoma. Clin Cancer Res 15:971-979, 2009

138. Jung HI, Jeong D, Ji S, et al: Overexpression of PD-L1 and PD-L2 is associated with poor prognosis in patients with hepatocellular carcinoma. Cancer Res Treat 49:246-254, 2017
139. El-Khoueiry AB, Melero I, Crocenzi TS, et al: Phase I/II safety and antitumor activity of nivolumab in patients with advanced hepatocellular carcinoma (HCC): CA209-040. J Clin Oncol 33, 2015. LBA101-LBA101
140. Melero I, Sangro B, Yau TC, et al: Nivolumab dose escalation and expansion in patients with advanced hepatocellular carcinoma (HCC): The CheckMate 040 study. J Clin Oncol 35:226, 2017
141. El-Khoueiry AB, Melero I, Yau TC, et al: Impact of antitumor activity on survival outcomes, and nonconventional benefit, with nivolumab (NIVO) in patients with advanced hepatocellular carcinoma (aHCC): Subanalyses of CheckMate-040. J Clin Oncol 36:475, 2018
142. Finn RS, Chan SL, Zhu AX, et al: KEYNOTE-240: Randomized phase III study of pembrolizumab versus best supportive care for second-line advanced hepatocellular carcinoma. J Clin Oncol 35:TPS503, 2017
143. Zhu AX, Finn RS, Edeline J, et al: Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): A non-randomised, open-label phase 2 trial. Lancet Oncol 19:940-952, 2018
144. Abou-Alfa GK, Chan SL, Furuse J, et al: A randomized, multicenter phase 3 study of durvalumab (D) and tremelimumab (T) as first-line treatment in patients with unresectable hepatocellular carcinoma (HCC): HIMALAYA study. J Clin Oncol 36:TPS4144, 2018
145. Chen X, Du Y, Hu Q, et al: Tumor-derived CD4+CD25+regulatory T cells inhibit dendritic cells function by CTLA-4. Pathol Res Pract 213:245-249, 2017
146. Sawada Y, Yoshikawa T, Ofuji K, et al: Phase II study of the GPC3-derived peptide vaccine as an adjuvant therapy for hepatocellular carcinoma patients. Oncoimmunology 5:e1129483, 2016
147. Cui J, Wang N, Zhao H, et al: Combination of radiofrequency ablation and sequential cellular immunotherapy improves progression-free survival for patients with hepatocellular carcinoma. Int J Cancer 134:342-351, 2014
148. Stein S, Pishvaian MJ, Lee MS, et al: Safety and clinical activity of 1L atezolizumab + bevacizumab in a phase Ib study in hepatocellular carcinoma (HCC). J Clin Oncol 36:4074, 2018
149. Ikeda M, Sung MW, Kudo M, et al: A phase 1b trial of lenvatinib (LEN) plus pembrolizumab (PEM) in patients (pts) with unresectable hepatocellular carcinoma (uHCC). J Clin Oncol 36:4076, 2018
150. Xing M, Kokabi N, Camacho JC, et al: Prospective longitudinal quality of life and survival outcomes in patients with advanced infiltrative hepatocellular carcinoma and portal vein thrombosis treated with Yttrium-90 radioembolization. BMC Cancer 18:75, 2018
151. Kolligs FT, Bilbao JI, Jakobs T, et al: Pilot randomized trial of selective internal radiation therapy vs. chemoembolization in unresectable hepatocellular carcinoma. Liver Int 35:1715-1721, 2015
152. Salem R, Gordon AC, Mouli S, et al: Y90 radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology 151:1155-1163.e2, 2016
153. Pitton MB, Kloeckner R, Ruckes C, et al: Randomized comparison of selective internal radiotherapy (SIRT) versus drug-eluting bead transarterial chemoembolization (DEB-TACE) for the treatment of hepatocellular carcinoma. Cardiovasc Intervent Radiol 38:352-360, 2015
154. Biederman DM, Titano JJ, Bishay VL, et al: Radiation segmentectomy versus TACE combined with microwave ablation for unresectable solitary hepatocellular carcinoma up to 3 cm: A propensity score matching study. Radiology 283:895-905, 2017
155. Lewandowski RJ, Kulik LM, Riaz A, et al: A comparative analysis of transarterial downstaging for hepatocellular carcinoma: Chemoembolization versus radioembolization. Am J Transplant 9:1920-1928, 2009
156. Lewandowski RJ, Donahue L, Chokechanachaisakul A, et al: 90Y radiation lobectomy: Outcomes following surgical resection in patients with hepatic tumors and small future liver remnant volumes. J Surg Oncol 114:99-105, 2016
157. Gabr A, Abouchaleh N, Ali R, et al: Comparative study of post-transplant outcomes in hepatocellular carcinoma patients treated with chemoembolization or radioembolization. Eur J Radiol 93:100-106, 2017
158. Pardo F, Sangro B, Lee R-C, et al: The post-SIR-Spheres Surgery Study (P4S): Retrospective analysis of safety following hepatic resection or transplantation in patients previously treated with selective internal radiation therapy with yttrium-90 resin microspheres. Ann Surg Oncol 24:2465-2473, 2017
159. Chow PHW, Gandhi M: Group A-PHCT. Phase III multi-centre open-label randomized controlled trial of selective internal radiation therapy (SIRT) versus sorafenib in locally advanced hepatocellular carcinoma: The SIRveNIB study. J Clin Oncol 35:4002, 2017
160. Vilgrain V, Pereira H, Assenat E, et al: Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): An open-label randomised controlled phase 3 trial. Lancet Oncol 18:1624-1636, 2017
161. Kennedy A, Brown DB, Feilchenfeldt J, et al: Safety of selective internal radiation therapy (SIRT) with yttrium-90 microspheres combined with systemic anticancer agents: Expert consensus. J Gastrointest Oncol 8:1079-1099, 2017
162. Salman A, Simoneau E, Hassanain M, et al: Combined sorafenib and yttrium-90 radioembolization for the treatment of advanced hepatocellular carcinoma. Curr Oncol 23:e472-e480, 2016
163. Kulik L, Vouche M, Koppe S, et al: Prospective randomized pilot study of Y90+/−sorafenib as bridge to transplantation in hepatocellular carcinoma. J Hepatol 61:309-317, 2014
164. Wehrenberg-Klee E, Goyal L, Dugan M, et al: Y-90 radioembolization combined with a PD-1 inhibitor for advanced hepatocellular carcinoma. Cardiovasc Intervent Radiol 41:1799-1802, 2018
165. Chang EWY, Tai DW-M, Koo S-L, et al: A phase II open-label, single-centre, non-randomized trial of Y90 transarterial radioembolization in combination with nivolumab in Asian patients with intermediate stage hepatocellular carcinoma: An immunological study of radioembolization in combination with anti-PD1 therapy in HCC. J Clin Oncol 36: TPS542, 2018